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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,069	09/25/2003	Tariq M. Rana	UMY-062RCE	4721

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,069	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,19,21,22,27,33-36,39-63 and 84-108* is/are pending in the application.

4a) Of the above claim(s) *19,21,22,27,34-36,40-63 and 91-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,33,39 and 84-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/07,8/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/13/2008 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 03/13/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 24 October 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 02/12/2007, claims 1, 3-4, 33, 39 and 84-90 are under examination and claims 19, 21-22, 27, 34-36, 40-63 and 91-108 are withdrawn from further consideration. Applicant has canceled claims 2, 5-18, 20, 23-26, 28-32, 37-38 and 64-83.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 22/44321 of record), Eckstein et al. (U.S. Patent No. 5,672,695 of record), Parrish et al. (cited on IDS filed 02/25/2006) and Allerson et al. (US 2005/0026160).

The instant claims are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA, wherein the antisense strand is modified by the substitution of each uridine with 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least 30% and wherein the siRNA further comprises a cleavage site for RISC and wherein the antisense strand is further modified by substitution of each adenosine and each guanosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site with deoxy adenosine and deoxy guanosine.

Tuschl et al. teach a siRNA, 19-25 nucleotides in length (see page 4, lines 1-4) wherein the siRNA comprise sugar or backbone modifications to increase *in vivo*

stability and teach a preferred embodiment wherein the 2'-OH group is modified with a 2'-fluoro group, for example (see page 6, lines3-6). Tuschl et al. teach gene silencing from eukaryotic, plant cells or viral-infected cells (see page 8, lines 11-19). Tuschl et al. teach the 3' ends can be modified by substitution of the 2 uridine nucleotides with 2'-deoxythymidine or with UU nucleotides (see page 48, lines 1-18). Tuschl et al. further teach a composition comprising a siRNA as described above and a pharmaceutical carrier (see page 9, lines 11-15). Tuschl et al. does not explicitly teach cytidine or uridine nucleotides in the antisense or sense strands having 2'-fluoro modifications nor specifically teach adenosine or guanosine nucleotides in the antisense or sense strands having 2' modifications. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules. Tuschl et al. appear to recognize that chemical modification of the 2'-OH is a result-effective variable that may enhance nuclease resistance on the one hand and modulate siRNA activity on the other. Furthermore, Tuschl et al. suggests several types of substituents that may be used to replace the 2'-OH group, namely 2'-fluoro (see page 6, lines 1-4).

Likewise, Eckstein et al. recognizes that chemical modifications of the 2' position of RNA is a result-effective variable and teach the 2' hydroxyl of a RNA molecule is susceptible to degradation by nucleases and modification of 2' hydroxyl position of the ribose sugar enhances the stability of RNA molecules (see column 2, lines 55-60). Eckstein et al. teach preferred modifications of the cytidine and uridine with 2'-fluoro analogues (see column 4, lines 9-25).

Parrish et al. teach a double stranded RNA capable of interfering with gene expression and teach incorporation of different chemical modifiers at the 2' position enhance the molecules specificity and specifically teach modification of nucleotides with a 2' fluoro group as well dsRNA with either the sense or antisense strands unmodified are capable of RNA interference (see Figures 5 and 6).

Allerson et al. teach siRNA comprising 2'-flouro groups as well as 2'-deoxynucleotides wherein the modified nucleotides are on the sense or antisense strand and further teach siRNA comprising various configurations and motifs of said nucleotides and teach said siRNA are capable of eliciting RNAi in cells (see Examples 1-7). Further, Allerson et al. teach said modified siRNA were capable of retaining activity up 86% compared to untreated controls (see for example paragraph 0365).

It would have been obvious to one of ordinary skill in the art at the time the invention was made and a matter of routine experimentation to use the general conditions taught by Tuschl et al. for making 2'-modified siRNA to discover the optimal number and placement of 2'-sugar modifications in any siRNA molecule, such that the resulting siRNA molecule was endowed with maximum stability and functionality. Additionally, it would have been obvious to one of ordinary skill in the art to incorporate known modifications, such as 2'-fluoro modifications of cytidine and uridine as taught by Eckstein et al. and 2'-deoxy nucleotide modifications as taught Parrish et al. and Allerson et al., to impart increased stability and functionality in any siRNA because it is well known to one of ordinary skill in the art that RNA has very low stability under

physiological conditions and therefore modifications of RNA will provide therapeutic RNA with enhanced stability against chemical and enzymatic degradation.

One would have been motivated to create such compounds with increased stability and functionality, and since siRNAs are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function in culture and in whole organisms (paragraphs 29-30), which may be considered to be nuclease-rich environments. One would therefore be motivated to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. Further, one would have been motivated to search for particular chemical modifications by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the dsRNA and one would have been motivated to incorporate said modifications such that the maximum amount of RNAi activity is obtained compared to unmodified siRNA. Eckstein et al. provide motivation to substitute the 2' positions of cytidine and uridine in siRNA molecules with 2'-fluoro groups to improve the efficacy because Eckstein et al. teach such modifications slowed down the degradation of the RNA by nucleases (see column 3, lines 36-59).

It must be noted that the limitation in claim 86 reciting the substitution of each adenosine and guanosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site referencing the antisense strand with a 2'-deoxy adenosine or guanosine is given its reasonable broadest interpretation. Therefore,

because there is no specific sequence claimed, it is conceivable that a siRNA would not have an adenosine or guanosine located in the region of the cleavage site on the antisense strand and therefore the siRNA would not have any substitutions with a 2'-deoxy adenosine or guanosine. Further, the specification on page 14 defines the cleavage site as 8-12 nucleotides from the 5' end of the antisense strand, therefore the substitution of each adenosine or guanosine, depending on the sequence, could be from nucleotides 6 to 15 from the 5' end of the antisense strand. Given this breadth of possibilities of substitution of an adenosine or guanosine in the claimed siRNA, and given the different modifications shown by Parrish et al. and Allerson et al., one of skill in the art would have been motivated to search for particular chemical modifications by routine experimentation to determine the optimum number and placement of the 2'-fluoro and deoxynucleotide modifications in either the sense or antisense strand of a dsRNA that would enhance the molecules stability.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known and Parrish et al. and Eckstein et al. teach known 2'-fluoro modifications increase RNA nuclease resistance. Further Tuschl et al. teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein.

Thus, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

The rejection of claim 86 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 1, 3-4, 33, 39 and 84-90 under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 22/44321), Eckstein et al. (U.S. Patent No. 5,672,695) and Parrish et al. (cited on IDS filed 02/25/2006) is maintained for the reasons of record in the Office action mailed 02/12/2007 and extended to the claims as modified in claim 1.

Applicant's arguments filed 03/13/2008 have been fully considered but they are not persuasive. Applicant argues Tuschl et al. fail to teach or suggest the specific sugar-modified ribonucleotides as claims and fails to teach the specific combinations and positions of these sugar-modified ribonucleotides with a siRNA. Applicant further argues Tuschl et al. teach away from the claimed invention and points to support for this argument at page 5, lines 16-20 wherein Tuschl et al. states "mismatches in the center of the siRNA duplex are most critical and essentially abolish target RNA cleavage." From this statement, Applicant argues one of skill would simply not have been motivated based on Tuschl et al. to introduce nucleotide analogues at internal positions. This argument is not convincing. As stated in the previous Office action, Tuschl et al.

does not explicitly teach cytidine or uridine nucleotides in the antisense or sense strands having 2'-fluoro modifications nor any specific configuration of these modified nucleotides but given nor Tuschl et al. clearly recognized that 2'-modifications enhance the nuclease stability of siRNA molecules, it would have been obvious to try various modifications to make compounds with increased stability and functionality. Moreover, Applicants appear to misinterpret the statement by Tuschl et al. regarding modifications in the center of the siRNA duplex. Tuschl et al. states *mismatches* i.e. nucleotides that are not complementary to the target strand, in the center of the duplex appear to abolish target RNA cleavage. Tuschl et al. does not make the statement that chemical modifications of internal positions in the duplex, as instantly claimed, abolish RNAi activity. Thus, as stated, it would have been obvious to try and a matter of routine optimization to incorporate 2'-modifications of the siRNA for increased duplex stability.

Applicant argues the teachings of Eckstein et al. fail to make up for the deficiencies of Tuschl et al. because the teachings are directed to ribozymes and one of skill in the art would not have been motivated to introduce the modified nucleosides taught by Eckstein et al. into siRNA because they are completely different molecules having different mechanisms of actions. This argument is not convincing. As stated by Eckstein et al. and well known to one of skill in the art, RNA has very low stability under physiological conditions and therefore modifications of nucleotides of RNA provide therapeutic RNA with enhanced stability against chemical and enzymatic degradation. Eckstein et al. provide motivation to substitute the 2' positions of cytidine and uridine in siRNA molecules with 2'-fluoro groups to improve the efficacy because Eckstein et al.

teach such modifications slowed down the degradation of the RNA by nucleases. Given that both ribozymes and siRNA are nucleic acids susceptible to nuclease degradation, one of skill in the art would have incorporated known chemical modifications that have proven to increase nuclease resistance to inhibitory RNA molecules, into siRNA to improve the stability of such molecules.

Applicant argues Parrish et al. fail to make up for the deficiencies of Tuschl et al. and teach away from the claimed invention because Parrish et al. teach deoxy modifications in the trigger strand are more sensitive to modification of the antisense strand than that of the sense strand. This argument is not convincing because both Parrish et al. and Tuschl et al. would lead one of ordinary skill in the art to try and incorporate various known chemical modifications in order to optimize the duplex to have optimum nuclease resistance and stability. All of the claimed chemical modifications are considered within the realm of routine optimization for the skilled artisan and the specific claimed combinations of modified siRNA are considered within the realm of routine optimization and are not considered unexpected as compared to the prior art.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention, and a matter of routine experimentation, to use the general conditions taught by Tuschl et al., Eckstein et al. and Parrish et al. for making 2'-modified siRNA to discover the optimal number and placement of 2'-sugar modifications in any siRNA molecule, such that the resulting siRNA molecule was endowed with maximum stability

and functionality such that the siRNA retains the ability to inhibit expression of the target mRNA by at least 30%. Therefore, the rejection of record is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Examiner
Art Unit 1635